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A Simulation Study Reveals Lack of Pharmacokinetic/Pharmacodynamic Target Attainment in De-escalated Antibiotic Therapy in Critically Ill Patients

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De-escalation of empirical antibiotic therapy is often included in antimicrobial stewardship programs in critically ill patients, but differences in target attainment when antibiotics are switched are rarely considered. The primary objective of this study was to compare the fractional target attainments of contemporary dosing of empirical broad-spectrum β-lactam antibiotics and narrower-spectrum antibiotics for a number pathogens for which de-escalation may be considered. The secondary objective was to determine whether alternative dosing strategies improve target attainment. We performed a simulation study using published population pharmacokinetic (PK) studies in critically ill patients for a number of broad-spectrum β-lactam antibiotics and narrower-spectrum antibiotics. Simulations were undertaken using a data set obtained from critically ill patients with sepsis without absolute renal failure ($n = 49$). The probability of target attainment of antibiotic therapy for different microorganisms for which de-escalation was applied was analyzed. EUCAST MIC distribution data were used to calculate fractional target attainment. The probability that therapeutic exposure will be achieved was lower for the narrower-spectrum antibiotics with conventional dosing than for the broad-spectrum alternatives and could drastically be improved with higher dosages and different modes of administrations. For a selection of microorganisms, the probability that therapeutic exposure will be achieved was overall lower for the narrower-spectrum antibiotics using conventional dosing than for the broad-spectrum antibiotics.

Provision of antibiotic therapy that is timely and of an appropriate spectrum is one of the mainstays of treatment (1, 2). This has led to the widespread use of broad-spectrum antibiotic therapy for the empirical treatment of infections. After identification of the causative microorganism, antibiotic therapy is typically adapted to the susceptibility profile of the microorganism, with a preference to change therapy to narrower-spectrum agents in order to decrease selective pressure for resistant pathogens. This process is called antibiotic de-escalation and is considered an important element in antibiotic stewardship programs (3–5).

Although the timing and adequacy of the antibiotic therapy remain crucial, recent data hint at the importance of antibiotic dosing and exposure on clinical outcome (6). Changes in the physiology of the critically ill alter the pharmacokinetics (PKs) of β-lactam antibiotics, with many patients being at risk of being underdosed (7, 8). Attainment of PK/pharmacodynamic (PD) targets associated with efficacy is also dependent on the susceptibility of the pathogen and varies across antibiotic classes, an element that is rarely considered (8).

Although de-escalation of antibiotic therapy is a key element in many antibiotic stewardship programs, the possible change in PK/PD target attainment in de-escalation has not yet been considered. De-escalation has been associated with improved outcomes in many observational (nonrandomized) studies; however, these findings may be due to selection bias, as de-escalation may be mainly performed in patients who are improving (9, 10). A recent randomized controlled study performed by Leone et al. (11) found that de-escalation to narrower-spectrum antibiotics did not reduce patient intensive care unit (ICU) length of stay and was associated with an increased number of antibiotic days in patients in whom antibiotic therapy had been de-escalated. The authors also reported that superinfections were more frequent in patients in whom antibiotic therapy had been de-escalated, with about half of the superinfections being caused by the same pathogens that caused the initial infection (11).

Based on these observations, we hypothesized that PK/PD target attainment after de-escalation may be lower than that with empirical therapy, even when the pathogen is reported to be susceptible to the de-escalation antibiotic. The primary objective of this study was to compare the probability that PK/PD targets will be achieved with conventional dosing of empirical broad-spectrum antibiotics and narrower-spectrum antibiotics for a number of pathogens for which de-escalation may occur. The secondary objective was to determine whether PK/PD target attainment could be improved with alternative dosing strategies for both types of antibiotics.

MATERIALS AND METHODS

We performed an *in silico* (computer) simulation study using published population pharmacokinetic studies in critically ill patients for a number of broad-spectrum β-lactam antibiotics (meropenem and piperacillin-

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TABLE 1 Simulated intravenous dosages of antibiotics

Antibiotic	Dosage simulation
Meropenem	1 g every 8 h as an intermittent infusion
	1 g every 8 h as a 4-h extended infusion
	3 g/day as a continuous infusion
Piperacillin	4 g every 8 h as an intermittent infusion
	4 g every 8 h as a 4-h extended infusion
	12 g/day as a continuous infusion
	4 g every 6 h as an intermittent infusion
	4 g every 6 h as a 3-h extended infusion
	16 g/day as a continuous infusion
Cefepime	1 g every 12 h as an intermittent infusion
	2 g every 12 h as an intermittent infusion for *S. aureus* infections
Amoxicillin	1 g every 6 h as an intermittent infusion
Cefuroxime	1.5 g every 8 h as an intermittent infusion
Flucloxacillin	1 g every 6 h as an intermittent infusion
Cefazolin	1 g every 8 h as an intermittent infusion

TABLE 2 Simulated dosages for the de-escalation antibiotics using higher dosages and alternative dosing strategies

Antibiotic	Dosage simulation
Amoxicillin	1 g every 4 h as an intermittent infusion
	1 g every 4 h as a 2-h extended infusion
	6 g/day as a continuous infusion
Cefuroxime	1.5 g every 6 h as an intermittent infusion
	1.5 g every 6 h as a 3-h extended infusion
	6 g/day as a continuous infusion
Flucloxacillin	2 g every 6 h as an intermittent infusion
	2 g every 6 h as a 3-h extended infusion
	8 g/day as a continuous infusion
Cefazolin	1 g every 6 h as an intermittent infusion
	1 g every 6 h as a 3-h extended infusion
	4 g/day as a continuous infusion
Cefepime	2 g every 8 h as an intermittent infusion
	1 g every 4 h as an intermittent infusion
	4 g/day as a continuous infusion

tazobactam) and narrower-spectrum antibiotics often used in de-escalation (amoxicillin-clavulanic acid, cefuroxime, flucloxacillin, cefazolin, and cefepime), as reported in recent studies (12–18). Protein binding was assumed to be 17% for amoxicillin, 33% for cefuroxime, and 10% for cefepime (19). Protein binding for meropenem is negligible, and the models for piperacillin, flucloxacillin, and cefazolin were based on measured free concentrations, so no correction was necessary.

We simulated 30-min infusions for all antibiotics, as intermittent infusion remains the most common method of administration in ICUs (6). Treatment with the broad-spectrum empirical antibiotics was also simulated as extended and continuous infusions, as these administration techniques are becoming more common as a way to maximize PK/PD target attainment (20). For amoxicillin-clavulanic acid and piperacillin-tazobactam, doses for the amoxicillin or piperacillin component only were simulated because the PK/PD targets for the β-lactamase inhibitors in these combinations remain unclear. The simulated dosages were derived from the package inserts and are summarized in Table 1. PK/PD target attainment of higher dosages and alternative dosing strategies were also investigated for the narrower-spectrum antibiotics. The simulated dosages are summarized in Table 2.

The simulations were performed using NONMEM (version 7.3.0; Globomax LLX, Hanover, MD, USA). A digital FORTRAN compiler was used, and the runs were executed using Wings for NONMEM (http://wfn.sourceforge.net). For each antibiotic, 1,000 Monte Carlo simulations were undertaken using a patient data set ($n = 49$) with various creatinine clearances (range, 22 to 230 ml/min) and the parameters from the published covariate model. This data set was obtained from a previous study conducted in a tertiary referral ICU (21). Patients were eligible for enrollment if they were between 18 and 80 years of age and were receiving piperacillin-tazobactam for the treatment of sepsis (defined as a presumed or confirmed infection, while manifesting a systemic inflammatory response syndrome). Patients were excluded if they did not have an intra-arterial line, had significant renal impairment (defined by a plasma creatinine concentration of >171 μmol/liter or the need for renal replacement therapy), or had a history of allergy to piperacillin or iodine. This therefore represents a convenience sample of critically ill septic patients without significant renal impairment. The patient characteristics are summarized in Table 3.

Using the simulated concentration-time profiles, the time for which the free antibiotic concentration exceeds the MIC ($fT_{>MIC}$) was calculated for each simulated subject using linear interpolation. The PK/PD target was set at 40% $fT_{>MIC}$ for carbapenems, 50% $fT_{>MIC}$ for penicillins, and 65% $fT_{>MIC}$ for cephalosporins, and this was defined as the conservative PK/PD target, which is the target found to be associated with the maximal effect in animal models (22). There are almost no data on which targets are needed to treat infections in critically ill patients; however, there are some retrospective studies that have found that higher targets may be needed to treat serious infections in this patient population. Therefore, we performed an additional simulation with a higher target of 100% $fT_{>MIC}$ for all antibiotics (23, 24).

The microorganisms used in this simulation study were *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus* spp., *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Citrobacter freundii*, *Morganella morganii*, and *Proteus mirabilis*, as these are microorganisms for which de-escalation is more commonly performed (9, 11, 25–27).

MIC distribution data for each antibiotic for the pathogens indicated above were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to determine fractional target attainment (FTA) (28). This identifies the likely success of treatment by comparing the achievement of the PK/PD target against an MIC distribution. Microorganisms with an MIC above the clinical susceptible breakpoint

TABLE 3 Patient characteristics[a]

Characteristic	Value
No. of males/no. of females	27/22
Age (yr)	46 (33–64)
Ht (m)	1.70 (1.63–1.80)
Wt (kg)	84 (73–95)
BMI (kg/m^2)	29.4 (25.1–33.3)
Creatinine clearance (ml/min)	105 (74–143)
APACHE II score	17 (14–25)
SOFA score	6 (5–9)
Serum urea concn (mmol/liter)	6.2 (3.9–8.7)
Serum creatinine concn (μmol/liter)	73 (55–97)
Serum albumin concn (g/liter)	21 (20–24)
8-h creatinine clearance (ml/min)	112 (76–142)
% of patients mechanically ventilated	93.4

[a] Unless indicated otherwise, data are reported as the median (interquartile range). BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment.

TABLE 4 FTA for different antibiotics, microorganisms, dosages, and modes of administration using the both the conservative and the high PK/PD targets[a]

		FTA (%)															
		Oxacillin-susceptible *S. aureus*		*Streptococcus* spp.		*K. pneumoniae*		*H. influenzae*		*C. freundii*		*M. morganii*		*P. mirabilis*		*E. coli*	
Antibiotic	Dosing	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Meropenem	3 g, CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	1 g q8h, EI	99	**87**	100	100	100	93	100	93	99	92	99	**89**	100	92	100	97
	1 g q8h, II	99	**64**	100	100	100	**72**	100	**73**	99	**70**	99	**66**	100	70	100	**88**
Piperacillin- tazobactam	16 g, CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	4 g q6h, EI	100	94	100	100	100	**87**	100	100	100	**88**	100	96	100	96	100	91
	4 g q6h, II	98	**87**	100	100	95	**76**	100	100	96	**78**	99	91	99	91	97	81
	12 g, CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	4 g q8h, EI	100	**88**	100	100	100	**77**	100	100	100	**79**	100	100	100	92	100	82
	4 g q8h, II	95	**78**	100	100	**89**	**62**	100	100	90	**65**	97	**83**	97	**84**	92	69
Cefepime	1 g q12h, II	**76**	**54**	100	97	100	99	100	99	100	100	100	100	100	100	100	100
	2 g q12h, II	**88**	**69**	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	2 g q8h, II	98	90	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	1 g q4h, II	99	98	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	4 g, CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Amoxicillin- clavulanic acid	1 g q6h, II	96[b]	**83**[b]	100[b]	100[b]	**90**	**77**	98[b]	**89**[b]	91	**74**	**89**[b]	**73**[b]	98	**87**	**85**	**66**
	1 g q4h, II	99[b]	92[b]	100[b]	100[b]	**95**	**86**	99[b]	97[b]	96	**86**	95[b]	**85**[b]	99	95	92	**80**
	1 g q4h, EI	100[b]	95[b]	100[b]	100[b]	95	90	100[b]	98[b]	100	90	100[b]	**89**[b]	100	97	100	**85**
	6 g, CI	100[b]	100[b]	100[b]	100[b]	99	99	100[b]	100[b]	99	99	98[b]	98[b]	100	100	98	98
Cefuroxime	1.5 g q8h, II	**86**	**61**	100	100	**73**	**53**	**88**	**71**	**66**	**46**			**83**	**64**	**65**	**45**
	1.5 g q6h, II	94	**81**	100	100	**84**	**67**	95	**84**	**79**	**61**			92	**78**	**78**	**60**
	1.5 g q6h, EI	99	90	100	100	95	**79**	100	92	93	**73**			99	**88**	92	**72**
	6 g CI	100	100	100	100	99	99	100	100	98	98			99	99	98	98
Flucloxacillin	1 g q6h, II	**74**	**36**														
	2 g q6h, II	**87**	**54**														
	2 g q6h, EI	100	**71**														
	8 g, CI	100	100														
Cefazolin	1 g q8h, II	90	**77**														
	1 g q6h, II	96	**89**														
	1 g q6h, EI	100	93														
	4 g, CI	100	100														

[a] Low, FTA using the conservative PK/PD target of 40% $fT_{>MIC}$ for carbapenems, 50% $fT_{>MIC}$ for penicillins, and 60% $fT_{>MIC}$ for cephalosporins; high, FTA using the high PK/PD target of 100% $fT_{>MIC}$; CI, continuous infusion; EI, extended infusion; II, intermittent infusion; q8h, every 8 h; q6h, every 6 h; q4h, every 4 h. Boldface indicates FTA of ≤90%.
[b] The MIC distribution of amoxicillin was used, as no MIC distribution of amoxicillin-clavulanic acid was available.

were not included in the FTA calculation because ongoing prescription would not be supported by the susceptibility testing upon which the de-escalation is based.

RESULTS

Probability of attainment for the conservative PK/PD target. The results of the simulations for the conservative target are shown in Table 4. The FTA for the conservative target for the broad-spectrum antibiotics administered as an intermittent infusion at high doses (piperacillin-tazobactam at 4 g every 6 h and meropenem at 1 g every 8 h) was >95% for all simulations, reaching 100% when administered as an extended or continuous infusion. The FTA for piperacillin-tazobactam at a lower dose (4 g every 8 h) was slightly lower, with the lowest FTA being 89% for *K. pneumoniae*, although this increased to 100% when administered as a continuous or extended infusion.

For the narrower-spectrum antibiotics in conventional dosing, the FTA was lower than that for the broad-spectrum antibiotics. As shown in Table 4, the FTA for amoxicillin-clavulanic acid (1 g every 6 h) ranged from 85% (*E. coli*) to 100% depending on the microorganism. The lowest FTA for cefuroxime (1.5 g every 8 h) was 65% for *E. coli*. Flucloxacillin (1 g every 6 h), cefepime (2 g every 12 h), and cefazolin (1 g every 8 h) had FTAs of, respectively, 74, 88, and 90% for oxacillin-susceptible *S. aureus*.

Probability of target attainment for the higher 100% $fT_{>MIC}$ target. The FTAs for the higher target of 100% $fT_{>MIC}$ are shown in Table 4. For the broad-spectrum antibiotics, only the continuous infusion of meropenem and piperacillin-tazobactam (piperacillin doses of 12 and 16 g/day) reached a 100% FTA for all studied microorganisms.

The FTA for meropenem (1 g every 8 h) administered as a

30-min infusion ranged from 100% (*Streptococcus* spp.) to 64% (oxacillin-susceptible *S. aureus*), which increased to 87% when administered as a 4-h infusion and to 100% when administered as a continuous infusion.

Similarly, for piperacillin-tazobactam, an increase in the infusion time improved the FTA. When administered at 4 g every 6 h, the lowest FTA was 76% for *K. pneumoniae*. It was 87% for the 3-h infusion and increased to 100% for the continuous infusion. At the lower dose, the FTA was only 62% for *K. pneumoniae*, 77% when administered as a 4-h extended infusion, and 100% when administered as a continuous infusion.

For the de-escalation antibiotics, the FTA was also lower than that for the conservative target. The lowest FTA for amoxicillin-clavulanic acid (1 g every 6 h) was 66% for *E. coli*, and the lowest FTA for cefuroxime was 45% for the standard dose of 1.5 g every 8 h for *E. coli*. The FTAs for flucloxacillin (1 g every 6 h) and cefepime (2 g every 12 h) for oxacillin-susceptible *S. aureus* were similarly poor (36% and 69%, respectively), but the FTA for cefazolin (1 g every 8 h) was slightly better at 77%.

Fractional target attainment when administering higher dosages or using alternative modes of administration for the narrower-spectrum antibiotics. The FTAs obtained using the conservative targets for the higher dosages/alternative modes of administration are shown in Table 4. Increasing the dose for amoxicillin-clavulanic acid from 1 g every 6 h to 1 g every 4 h increased the FTA using the conservative target for *E. coli* from 85% to 92%, and the FTA was increased to 100% when an extended or continuous infusion of 6 g was used. Similarly, for cefuroxime, increasing the dose and increasing the infusion time improved the FTA from 65% for *E. coli* (conventional dose of 1.5 g every 8 h) to 98% when administered as a continuous infusion of 6 g. For flucloxacillin, increasing the dose from 1 g every 6 h to 2 g every 6 h as an extended or continuous infusion increased the FTA for oxacillin-susceptible *S. aureus* from 74 to 100%. For cefazolin and cefepime, a continuous infusion of 4 g increased the FTA against oxacillin-susceptible *S. aureus* from 88% (cefepime at 2 g every 12 h) and 90% (cefazolin at 1 g every 8 h) to 100% for both antibiotics.

When using the higher target of 100% $fT_{>MIC}$, there were large differences in the FTAs between the broad- and narrower-spectrum antibiotics (Table 4). However, changing the intermittent infusion to a higher-dose continuous infusion improved the FTA dramatically. For amoxicillin-clavulanic acid, this improved the FTA from 66% (1 g every 6 h) to 98% (6 g continuously) for *E. coli*, and for cefuroxime, this improved the FTA from 45% (1.5 g every 8 h) to 98% (6 g continuously) for *E. coli*. For flucloxacillin, in order to obtain a high FTA for oxacillin-susceptible *S. aureus*, the dose needed to be increased from 1 g every 6 h (FTA, 36%) to 8 g as a continuous infusion (FTA, 100%), and for cefepime and cefazolin, the dose needed to be increased from 2 g every 12 h for cefepime (FTA, 69%) and 1 g every 8 h for cefazolin (FTA, 77%) to 4 g continuously (FTAs, 100%).

DISCUSSION

De-escalation of antibiotic therapy, or the changing of therapy with an empirical antibiotic to one with a narrower-spectrum antibiotic, is often advocated to reduce the use of broad-spectrum antibiotics in the hospitalized patient (3, 29). It is generally considered safe, has been associated with improved outcomes in several observational studies, and is recommended in the 2013 Surviving Sepsis Campaign guidelines (9, 10, 30). As such, it is often incorporated into antibiotic stewardship programs in critically ill patients (31, 32), although in clinical practice there seem to be a number of obstacles to its widespread use (33). In observational studies, empirical antibiotics are de-escalated in roughly 15 to 50% of the patients, depending on the definition used (9, 25, 33, 34).

In this study, we have found that for a number of pathogens, the fractional target attainment (FTA) was higher for the empirical broad-spectrum antibiotics meropenem and piperacillin-tazobactam than for the narrower-spectrum antibiotics amoxicillin-clavulanic acid, cefuroxime, flucloxacillin, cefazolin, and cefepime using conventional dosing. Given that the probability that the PK/PD target for some microorganism-antibiotic combinations will be achieved is lower for the narrower-spectrum alternative, de-escalation with standard dosing may predispose selected patients to clinical failure and recurrent infection. To the best of our knowledge, this is the first study of its kind to compare the achievement of therapeutic exposure by empirical antibiotic therapy with the achievement of therapeutic exposure by de-escalation of antibiotic therapy on the basis of population PK models from critically ill patients. Although there is currently no evidence that subtherapeutic dosing of β-lactam antibiotics leads to treatment failure or to a higher incidence of resistance, this has been shown for other antibiotics. For tobramycin, for example, it has been shown that although the peak concentration/MIC is associated with the maximal effect, for the same area under the curve/MIC value, once-daily dosing (with subsequent lower trough concentrations) leads to higher MIC values than three-times-daily dosing after 2 weeks of treatment (35).

The FTA is dependent on a number of factors, and recent insights into PK/PD characteristics in critically ill patients may help us to explain these findings. Because of pathophysiological changes in critically ill patients, such as an increased volume of distribution and augmented renal clearance, standard dosing may not always lead to optimal target attainment (36, 37). Moreover, it is also dependent on the PK/PD target (40% $fT_{>MIC}$ for carbapenems versus 65% $fT_{>MIC}$ for cephalosporins). Next, the susceptibility of the microorganism plays an important role. The susceptibility of the same microorganism may vary for different antibiotics, and similarly, the potencies of certain antibiotics against different microorganisms may be different, even though all microorganisms are reported to be susceptible (38). Moreover, the PK/PD target is currently considered to be fixed; however, it has never been investigated if the PK/PD target changes over time. A changing PK/PD target over time, not taken into account by dosing, could also result in treatment failure and the emergence of resistance. Finally, an increasing proportion of ICUs are administering meropenem and piperacillin-tazobactam as an extended or continuous infusion, as a way to increase PK/PD target attainment (6, 20). However, these alternative modes of administration are not used for the narrower-spectrum antibiotics, which are still being administered as short infusions with standard doses (6). This contrasting approach could further increase the gap in PK/PD target attainment between empirical and de-escalated antibiotic therapy.

The findings of our study may partly explain the findings of a recent de-escalation study that could not confirm noninferiority when comparing de-escalation to continuation of the empirical therapy (11). Leone et al. (11) found in a randomized controlled trial not carried out in a blind manner that antibiotic use was higher in patients in whom therapy had been de-escalated due to

an increased number of superinfections, about half of which were caused by the same pathogen that caused the primary infection. This suggests that the antibiotics used in the de-escalation arm were less effective in eradicating the infection than the broad-spectrum antibiotics in the comparative arm. In that study, no details regarding dosing were reported (11).

Of the most recent de-escalation studies, only one has mentioned the dose and mode of administration of the initial broad-spectrum regimen, but it did not mention these data about the de-escalated antibiotics (11, 25–27). Another study mentioned that "the dose and pattern of administration were in accordance with current medical standards" (9). Dosing may be the key to improve patient outcome, as recent data have demonstrated that there is a correlation between the blood concentrations of β-lactam antibiotics and clinical outcome (6). Future de-escalation studies should ensure that dosing and the mode of administration of the narrower-spectrum antibiotics are likely to achieve appropriate PK/PD targets.

We could also demonstrate that PK/PD target attainment is drastically improved when higher dosages and different modes of administration of the de-escalation antibiotics are used. However, it must also be highlighted that blindly increasing the dose in all patients may give rise to needlessly high concentrations in some of them. Although β-lactams are not commonly toxic, toxicity is severe when it occurs, with seizures from high concentrations being reported previously (39–41). This wide pharmacokinetic variability suggests that the principle of one dose fits all is unlikely to be appropriate in this patient population (42).

There are a number of limitations of the current analysis that we would like to discuss. These results are not based on measured concentrations from actual patients. However, we have simulated concentrations using population pharmacokinetic models and relevant covariates in critically ill patients. As such, the accuracy of the results can be assumed to be acceptable, given that the same approach was used for simulations with the empirical and de-escalation antibiotic. The patient population simulated consisted of patients who had normal renal function (serum creatinine concentration, <171 μmol/liter) and did not include patients with acute kidney injury, and therefore, these conclusions are relevant only to this patient group. Also, there is little knowledge on which PK/PD target should be aimed for in critically ill patients, as the targets are derived from animal models on day 1 or 2 of antibiotic therapy. Whether or not this PK/PD target changes over time as a result of the changing susceptibility or the adaptive resistance of the pathogen is also a remaining question. Moreover, there is no time dependency of the data. In clinical practice, de-escalation is generally performed when the patient is improving (and therefore, the pharmacokinetic issues associated with critical illness may be partly normalized) and has a lower bacterial burden. This cannot be accounted for in the modeling. Finally, only 7 antibiotics were simulated, due to the unavailability of population pharmacokinetic models of other β-lactam antibiotics in critically ill patients, although these are all commonly used agents, making these data of significant interest to many ICU clinicians.

Conclusion. For a selection of microorganisms in which de-escalation may be considered, the results of this simulation study show that the probability that the PK/PD target will be achieved was lower for the narrower-spectrum antibiotics amoxicillin-clavulanic acid, cefuroxime, flucloxacillin, cefazolin, and cefepime using conventional dosing than the broad-spectrum antibiotics meropenem and piperacillin-tazobactam. As this may impact clinical outcome parameters, studies that report on the results of de-escalation strategies should accurately report the dosing of the antibiotics used. Future research should be focused on correct dosing not only of broad-spectrum antibiotics but also of narrower-spectrum antibiotics, where higher dosages and alternative modes of administration may be needed for patients at risk of not achieving PK/PD targets.

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REFERENCES

1. **Rello J, Gallego M, Mariscal D, Sonora R, Valles J.** 1997. The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med **156:**196–200. http://dx.doi.org/10.1164/ajrccm.156.1.9607030.
2. **Kumar A, Roberts D, Wood K, Light B, Parrillo J, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M.** 2006. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **34:**1589–1596. http://dx.doi.org/10.1097/01.CCM.0000217961.75225.E9.
3. **Masterton RG.** 2011. Antibiotic de-escalation. Crit Care Clin **27:**149–162. http://dx.doi.org/10.1016/j.ccc.2010.09.009.
4. **DePestel DD, Eiland EH, III, Lusardi K, Destache CJ, Mercier RC, McDaneld PM, Lamp KC, Chung TJ, Hermsen ED.** 2014. Assessing appropriateness of antimicrobial therapy: in the eye of the interpreter. Clin Infect Dis **59**(Suppl 3)**:**S154–S161. http://dx.doi.org/10.1093/cid/ciu548.
5. **Trivedi KK, Dumartin C, Gilchrist M, Wade P, Howard P.** 2014. Identifying best practices across three countries: hospital antimicrobial stewardship in the United Kingdom, France, and the United States. Clin Infect Dis **59**(Suppl 3)**:**S170–S178. http://dx.doi.org/10.1093/cid/ciu538.
6. **Roberts J, Paul S, Akova M, Bassetti M, De Waele J, Dimopoulos G, Kaukonen K-M, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J.** 2014. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis **58:**1072–1083. http://dx.doi.org/10.1093/cid/ciu027.
7. **Roberts J, Lipman J.** 2009. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med **37:**840–851. http://dx.doi.org/10.1097/CCM.0b013e3181961bff.
8. **De Waele JJ, Lipman J, Akova M, Bassetti M, Dimopoulos G, Kaukonen M, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Udy AA, Starr T, Wallis SC, Roberts JA.** 2014. Risk factors for target non-attainment during empirical treatment with beta-lactam antibiotics in critically ill patients. Intensive Care Med **40:**1340–1351. http://dx.doi.org/10.1007/s00134-014-3403-8.
9. **Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernandez-Delgado E, Herrera-Melero I, Ortiz-Leyba C, Marquez-Vacaro JA.** 2014. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med **40:**32–40. http://dx.doi.org/10.1007/s00134-013-3077-7.
10. **Timsit JF, Harbarth S, Carlet J.** 2014. De-escalation as a potential way of

reducing antibiotic use and antimicrobial resistance in ICU. Intensive Care Med **40:**1580–1582. http://dx.doi.org/10.1007/s00134-014-3485-3.
11. **Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanese J, Jaber S, Lepape A, Constantin JM, Papazian L, Bruder N, Allaouchiche B, Bezulier K, Antonini F, Textoris J, Martin C, AZUREA Network Investigators.** 2014. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med **40:**1399–1408. http://dx.doi.org/10.1007/s00134-014-3411-8.
12. **Carlier M, Noë M, De Waele JJ, Stove V, Verstraete AG, Lipman J, Roberts JA.** 2013. Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients. J Antimicrob Chemother **68:**2600–2608. http://dx.doi.org/10.1093/jac/dkt240.
13. **Carlier M, Noe M, Roberts JA, Stove V, Verstraete AG, Lipman J, De Waele JJ.** 2014. Population pharmacokinetics and dosing simulations of cefuroxime in critically ill patients: non-standard dosing approaches are required to achieve therapeutic exposures. J Antimicrob Chemother **69:**2797–2803. http://dx.doi.org/10.1093/jac/dku195.
14. **Ulldemolins M, Roberts JA, Wallis SC, Rello J, Lipman J.** 2010. Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacokinetics. J Antimicrob Chemother **65:**1771–1778. http://dx.doi.org/10.1093/jac/dkq184.
15. **Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J.** 2009. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution J Antimicrob Chemother **64:**142–150. http://dx.doi.org/10.1093/jac/dkp139.
16. **Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K, Kirkpatrick CMJ, Kruger PS, Paterson DL, Roberts MS, Roberts JA.** 2014. Piperacillin target attainment in critically ill septic patients: are standard doses sufficient in the presence of augmented renal clearance? Crit Care **19:**28. http://dx.doi.org/10.1186/s13054-015-0750-y.
17. **Roberts JA, Udy AA, Jarrett P, Wallis SC, Hope WW, Sharma R, Kirkpatrick CM, Kruger PS, Roberts MS, Lipman J.** 2015. Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of cefazolin in post-trauma critically ill patients. J Antimicrob Chemother **70:**1495–1502. http://dx.doi.org/10.1093/jac/dku564.
18. **Roos JF, Bulitta J, Lipman J, Kirkpatrick CM.** 2006. Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units. J Antimicrob Chemother **58:**987–993. http://dx.doi.org/10.1093/jac/dkl349.
19. **Norrby SR.** 2010. *In* Grayson LM (ed), Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic and antiviral drugs, p 65–92, 286–294, 427–441, 6th ed, vol 1. Edward Arnold, London, United Kingdom.
20. **Buyle FM, Decruyenaere J, De Waele J, Tulkens PM, Van Audenrode T, Depuydt P, Claeys G, Robays H, Vogelaers D.** 2013. A survey of beta-lactam antibiotics and vancomycin dosing strategies in intensive care units and general wards in Belgian hospitals. Eur J Clin Microbiol Infect Dis **32:**763–768. http://dx.doi.org/10.1007/s10096-012-1803-7.
21. **Roberts J, Roberts M, Semark A, Udy A, Kirkpatrick C, Paterson D, Roberts M, Kruger P, Lipman J.** 2011. Antibiotic dosing in the 'at risk' critically ill patient: linking pathophysiology with pharmacokinetics/pharmacodynamics in sepsis and trauma patients. BMC Anesthesiol **11:**3. http://dx.doi.org/10.1186/1471-2253-11-3.
22. **Craig WA.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis **26:**1–10. http://dx.doi.org/10.1086/516284.
23. **McKinnon P, Paladino J, Schentag J.** 2008. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents **31:**345–351. http://dx.doi.org/10.1016/j.ijantimicag.2007.12.009.
24. **Li C, Du X, Kuti JL, Nicolau DP.** 2007. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother **51:**1725–1730. http://dx.doi.org/10.1128/AAC.00294-06.
25. **Mokart D, Slehofer G, Lambert J, Sannini A, Chow-Chine L, Brun JP, Berger P, Duran S, Faucher M, Blache JL, Saillard C, Vey N, Leone M.** 2014. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. Intensive Care Med **40:**41–49. http://dx.doi.org/10.1007/s00134-013-3148-9.
26. **Khasawneh FA, Karim A, Mahmood T, Ahmed S, Jaffri SF, Mehmood M.** 2014. Safety and feasibility of antibiotic de-escalation in bacteremic pneumonia. Infect Drug Resist **7:**177–182. http://dx.doi.org/10.2147/IDR.S65928.
27. **Kim J, Chung J, Choi S-H, Jang H, Hong S-B, Lim C-M, Koh Y.** 2012. Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. Crit Care **16:**R28. http://dx.doi.org/10.1186/cc11197.
28. **EUCAST.** 2012. Antimicrobial wild type distributions of microorganisms. EUCAST, Växjö, Sweden. http://mic.eucast.org/Eucast2/.
29. **Dodds Ashley ES, Kaye KS, DePestel DD, Hermsen ED.** 2014. Antimicrobial stewardship: philosophy versus practice. Clin Infect Dis **59**(Suppl 3)**:**S112–S121. http://dx.doi.org/10.1093/cid/ciu546.
30. **Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup.** 2013. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med **39:**165–228. http://dx.doi.org/10.1007/s00134-012-2769-8.
31. **Anonymous.** 2010. ASHP statement on the pharmacist's role in antimicrobial stewardship and infection prevention and control. Am J Health Syst Pharm **67:**575–577. http://dx.doi.org/10.2146/sp100001.
32. **Pollack LA, Srinivasan A.** 2014. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis **59**(Suppl 3)**:**S97–S100. http://dx.doi.org/10.1093/cid/ciu542.
33. **De Waele JJ, Bassetti M, Martin-Loeches I.** 2014. Impact of de-escalation on ICU patients' prognosis. Intensive Care Med **40:**1583–1585. http://dx.doi.org/10.1007/s00134-014-3488-0.
34. **Kollef MH.** 2006. Providing appropriate antimicrobial therapy in the intensive care unit: surveillance vs. de-escalation. Crit Care Med **34:**903–905. http://dx.doi.org/10.1097/01.CCM.0000202128.30405.60.
35. **Burkhardt O, Lehmann C, Madabushi R, Kumar V, Derendorf H, Welte T.** 2006. Once-daily tobramycin in cystic fibrosis: better for clinical outcome than thrice-daily tobramycin but more resistance development? J Antimicrob Chemother **58:**822–829. http://dx.doi.org/10.1093/jac/dkl328.
36. **Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, Lipman J, Roberts JA.** 2012. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest **142:**30–39. http://dx.doi.org/10.1378/chest.11-1671.
37. **Carlier M, Carrette S, Roberts J, Stove V, Verstraete A, Hoste E, Decruyenaere J, Depuydt P, Lipman J, Wallis S, De Waele J.** 2013. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care **17:**R84. http://dx.doi.org/10.1186/cc12705.
38. **Kapoor G, Saigal S.** 2014. De-escalation in severe sepsis: still an important part of our armamentarium against antimicrobial resistance. Intensive Care Med **40:**1618. http://dx.doi.org/10.1007/s00134-014-3476-4.
39. **Smith NL, Freebairn RC, Park MA, Wallis SC, Roberts JA, Lipman J.** 2012. Therapeutic drug monitoring when using cefepime in continuous renal replacement therapy: seizures associated with cefepime. Crit Care Resusc **14:**312–315.
40. **Gangireddy VG, Mitchell LC, Coleman T.** 2011. Cefepime neurotoxicity despite renal adjusted dosing. Scand J Infect Dis **43:**827–829. http://dx.doi.org/10.3109/00365548.2011.581308.
41. **Lam S, Gomolin IH.** 2006. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy **26:**1169–1174. http://dx.doi.org/10.1592/phco.26.8.1169.
42. **Beumier M, Casu GS, Hites M, Wolff F, Cotton F, Vincent JL, Jacobs F, Taccone FS.** 2015. Elevated beta-lactam concentrations are associated with neurological deterioration in ICU septic patients. Minerva Anestesiol **81:**497–506.